

REMARKS

Claims 1-3, 5-6, 9-11, 19-21, 23-24, and 27-29 are pending.

**I. Rejection under 35 U.S.C. § 112, 1<sup>st</sup> paragraph**

Examiner rejects claims 19-21, 23-24 and 27-29 as failing to comply with the requirements of 35 U.S.C. § 112, 1<sup>st</sup> paragraph. Applicant has cured such defect by way of amendment and respectfully requests Examiner withdraw the rejection of record with respect to these claims.

**II. Rejection under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph**

Examiner has rejected claims 11 and 29 as indefinite as to the composition makeup of the recited composition of independent claims 1 and 19. Applicant respectfully submits claim 11 as properly limiting the scope of claim 1, which recites a Markush-type limitation to the listed elements. Claim 11 merely limits this by having an additional limitation. This adds an additional limiting step and is proper under the Rules. The rejection is moot as applied to claim 29, as it has been canceled by way of amendment. Application respectfully requests Examiner withdraw the rejection of record with respect to these claims.

**II. Rejections under 35 U.S.C. §103**

Examiner rejects all claims as being unpatentable over Hewitt et al., Lozada and Sharpe et al., in view of Batt et al. Examiner alleges the employment of these teachings concomitantly in a method useful for the very same purpose

would be seen as prima facie obvious, absent evidence to the contrary. For the reasons submitted below, Applicant respectfully traverses Examiner's rejection and requests Examiner withdraw the §103 rejection, as there is no suggestion or motivation to combine the cited references and the references in fact teach away from the present application.

Applicant cites the arguments already of record against Examiner maintaining the §103(a) rejection. Further, Applicant respectfully directs Examiner's attention to the details within each of the cited references to support the notion that these references actually teach away from the present invention and one of ordinary skill in the art, upon reviewing these references, would not be motivated to combine same to arrive at the present invention.

**Hewitt et al. ("Hewitt")**

Hewitt mentions azathioprine only twice in the entire body of the specification; once for suggesting that cyclosporine administration prior to kidney allograft transplantation required minimal systemic azathioprine immunosuppression (see *Hewitt*, col. 2, lines 53-56) and once while disclosing examples of other agents that could analogously be combined with novel microorganism derived immunosuppressants in a single topical formulation (See *Hewitt*, col. 15, lines 5-14). Hewitt is silent on use of azathioprine alone for treatment of GvHD. More importantly, Hewitt cannot be said to motivate one of skill in the art to combine with any of the other references to

arrive at the present invention. Hewitt is focused primarily on using cyclosporine as a representative anti-inflammatory composition to induce site-specific immunosuppression in combination with other elements. This has little to do with the invention of the present application.

#### **Lozada**

Lozada analyzes the synergistic effect of azathioprine with prednisone for vesiculoerosive oral diseases. Lozada is silent on treatment with azathioprine itself. In fact, the principle point addressed in the study was to determine an alternate strategy to course of corticosteroid administration alone. The azathioprine was used as a means of reducing the effect of prednisone treatment alone, which is quite different to that suggested in the present application. Lozada goes so far as to state that "treatment with an immunosuppressant alone during the acute stage of MMP has shown itself to be inferior to the combined treatment with prednisone." (Lozada, p.259) Thus, one of relevant skill in the art could not arrive at the present invention, which teaches use of an immunosuppressant alone (azathioprine) for treatment of oral GvHD, as Lozada would be seen as teaching away from that proposed in the present application.

#### **Sharpe et al. ("Sharpe")**

Sharpe focuses on a method for treating diseases mediated by proteases. Sharpe is silent on oral GvHD and use of azathioprine to treat same. Sharpe merely suggests

a swishing mode of oral administration to treat various oral diseases. However, Sharpe is limited to administration of N-acetylcysteine, which is completely unrelated to azathioprine or like compounds. One of relevant skill in the art would not be motivated to combine Sharpe with any of the other references to do the lack of relationship between the treatment composition and the types of diseases.

**Batt et al. ("Batt")**

Batt discloses the then-present state of the art in treatment for various organ transplant rejections using immunosuppressive agents in combination with other adjunctive therapies, including azathioprine and corticosteroids (See *Batt*, col. 1, lines 33-37). However, the Batt teaches away from that described in the present application, as Batt discloses use of any of these known immunosuppressive compounds, including azathioprine, either alone or in combination, as being associated with a high risk of dangerous side effects, including nephrotoxicity and/or hepatotoxicity. Therefore, one of skill in the art would neither be motivated to combine with any of the references listed supra, nor be under any suggestion to try azathioprine alone in treating oral GvHD in light of the disclosed side effects of such immunosuppressive-only therapies.

None of the cited references mention treatment using azathioprine alone and, in fact, the references describe the necessity of a combined therapy of corticosteroid + immunosuppressant or, at the very least, treatment using


the corticosteroid alone. The above references were silent on treatment protocols involving only the immunosuppressant.

Therefore, Applicant respectfully requests Examiner withdraw the §103 rejection. There would be no motivation for one skilled in the art to combine the listed references, as these teach away from use of azathioprine alone for treatment of graft versus host, especially in the manner described in the present application.

Applicant respectfully requests withdrawal of the above identified rejections and allowance of the present application based on Applicant's arguments and amendments. No fees are believed due as this response is being timely filed. However, authorization is granted to charge any underpayments to Deposit Account No. 502235. If there are any questions or comments, Applicant's attorney may be reached at the telephone number state below.

Respectfully submitted,

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